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ENDORAMA

Management of Endocrine Pathology in Patients with VHL

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Jan 21, 2021

Dr. Stratton does not have any relevant financial relationships with any commercial interests.

Learning Objectives

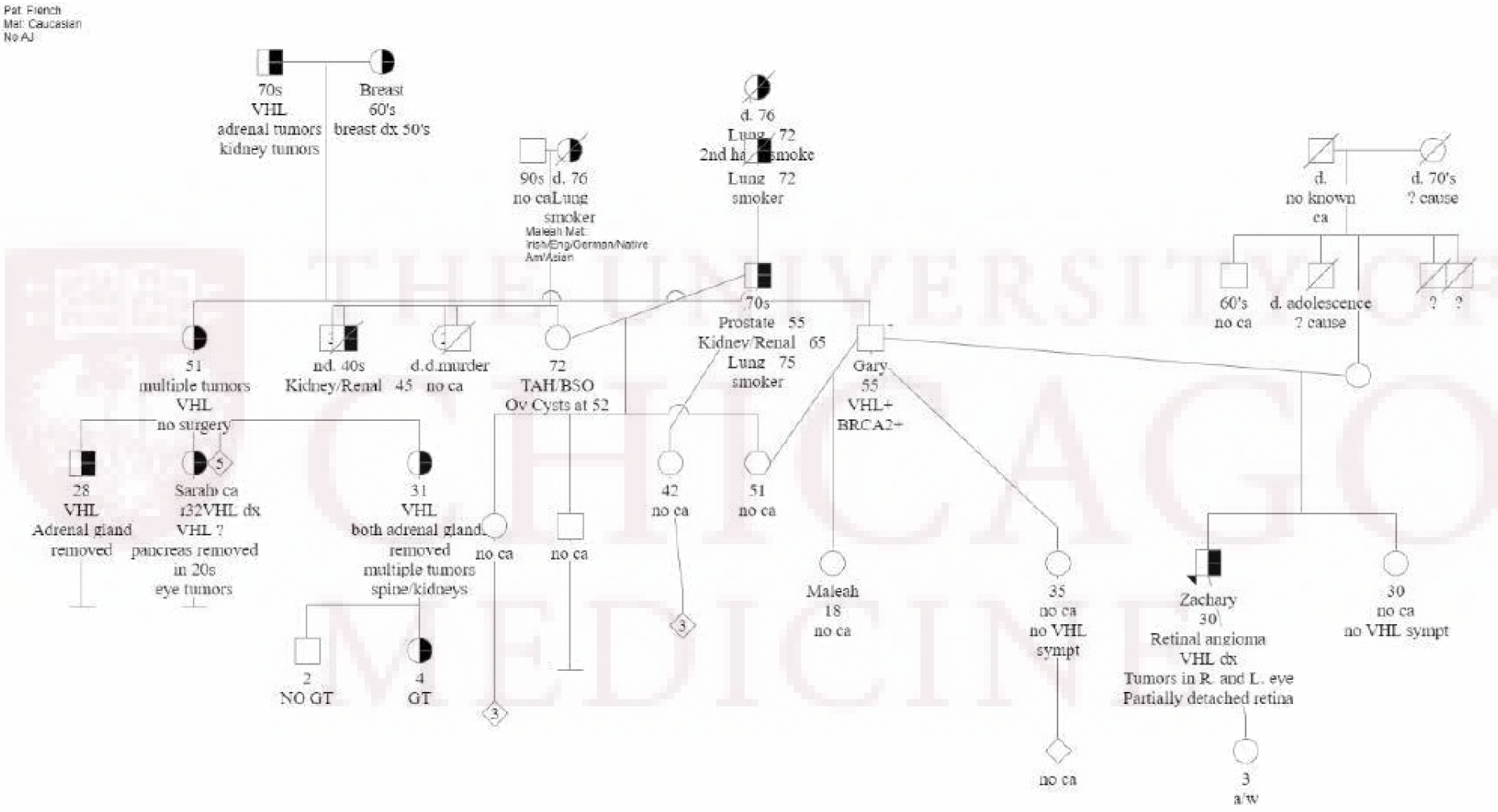
- Phenotypes of VHL patients
- Management of PNET and Pheochromocytomas in patients with VHL
- VHL Surveillance Strategies

Case Description

- 29 y/o M who presents with decreased vision in right eye on screening exam at work. Gradual decrease in vision over time, occasionally blurry with floaters.
- PMH/PSH: None
- FH: strong history of VHL
- SH: works as a truck driver, lives in Reno, NV

Case Description

- Optho: diagnosed with bilateral retinal capillary hemangiomas in 7/2019. Focal laser therapy monthly to smaller lesions
- Established care in VHL clinic here in 2020
- Genetic Testing: VHL positive



Clinical Diagnosis of VHL

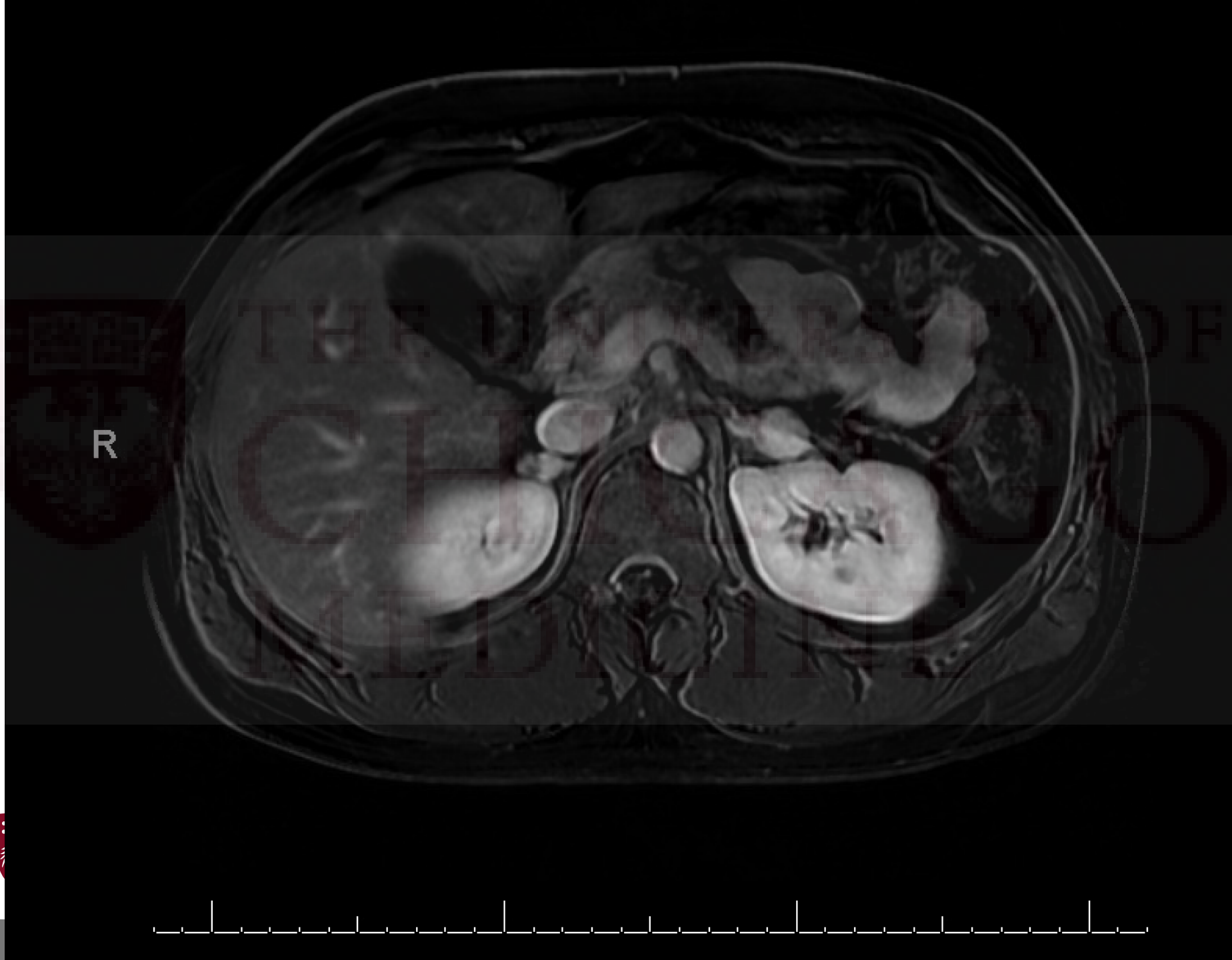
- An individual in whom two or more characteristic lesions are present (e.g. hemangioblastomas of the retina or brain, or a single hemangioblastoma in association with another cystic manifestation).
- An asymptomatic individual with a family history of confirmed VHL in whom one or disease manifestations is present
  - retinal angioma, spinal or cerebellar hemangioblastoma, pheochromocytoma, multiple pancreatic cysts, epididymal cystadenoma, multiple renal cysts, or renal cell carcinoma before age 60 years.

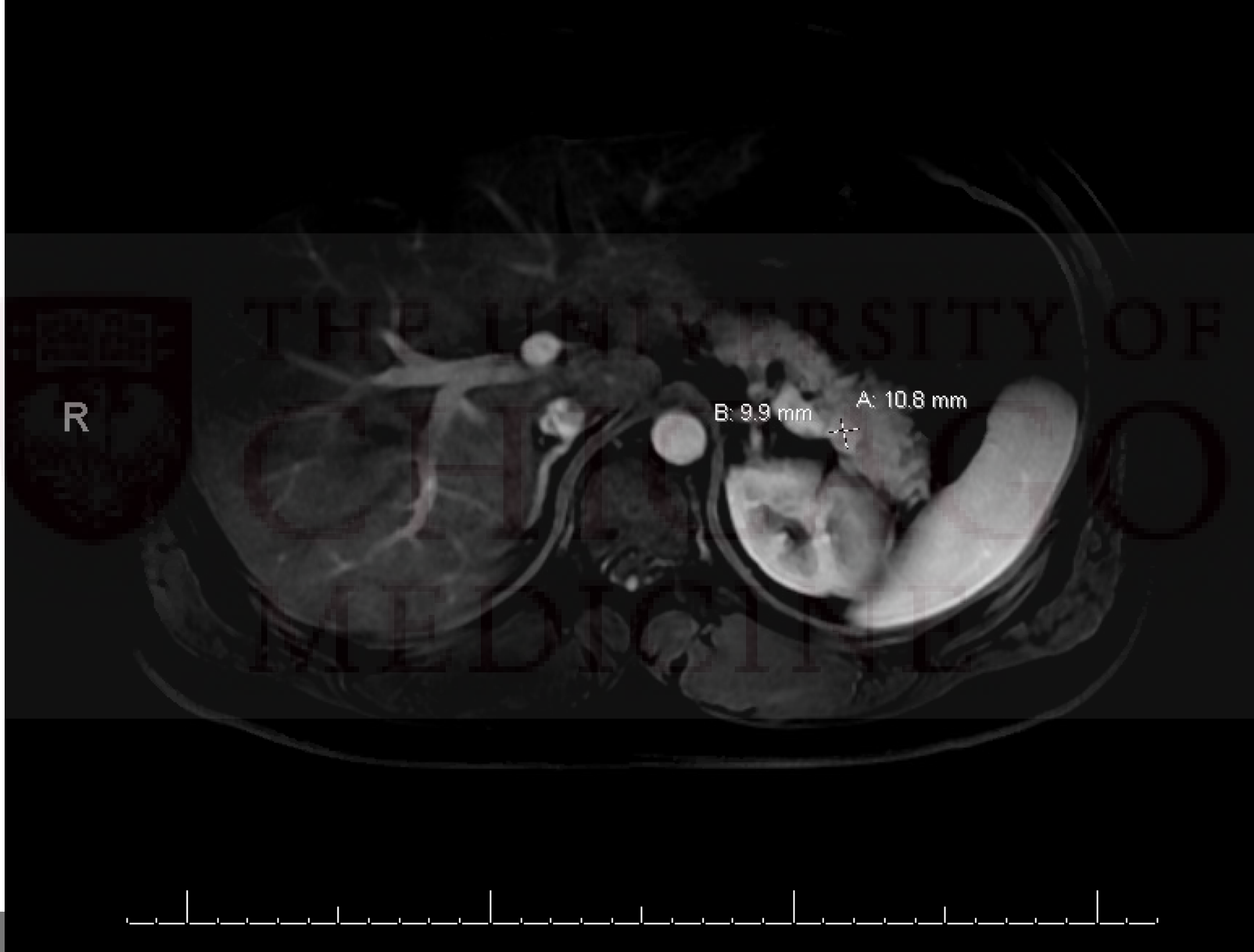
Imaging

- MRI Brain and Spine: multiple hemangioblastomas (cerebellum, right globe, multiple throughout spine)
- MRI Abdomen:
  *Pancreas: 0.8 x 1.1 x 1.0 cm hyperenhancing lesion in the pancreatic tail + 4mm cystic lesion suggestive of pNET

  *2.2 x 1.6 cm left adrenal gland nodule, 0.8cm separate L adrenal gland nodule and 0.7 x 0.7 cm right adrenal gland nodule, both of which do not have imaging characteristics of lipid rich adenomas and in a patient with VHL are suspicious for pheochromocytomas.

  *R kidney: 2.1x2.2cm lesion in R lower pole and *L kidney: 1.4cm x 1.3cm, 0.8cm lesions concerning for renal cell carcinoma


R


R
B: 9.9 mm
A: 10.8 mm

Labs

- Plasma Metanephrines: 0.22
- Plasma Normetanephrines: **2.44 (x2.7 ULN)**
- Plasma Epinephrine: 51
- Plasma Norpepinephrine: **1360 (x2.6 ULN)**
- Symptoms: frequent headaches, easy irritability, panic attacks and spells of dizziness over the past few years. He does not check his BP regularly.

Plasma Metanephrines vs 24 Hour Urine

- Send out lab (Mayo): high-performance liquid chromatography (HPLC) with electrochemical detection or tandem mass spectroscopy (MS/MS)
- 2014 Endocrine Society clinical practice guideline: initial biochemical testing using 24-hour urinary fractionated metanephrines or plasma fractionated metanephrines (drawn supine with an indwelling cannula for 30 minutes)
- Low index of suspicion: 24 hr urine
- Plasma metanephrines: higher sensitivity but slightly higher false-positive rate

Medications that may increase measured levels of catecholamines and metanephrines

Tricyclic antidepressants
Levodopa
Drugs containing adrenergic receptor agonists (eg, decongestants)
Amphetamines
Buspirone and most psychoactive agents
Prochlorperazine
Reserpine
Withdrawal from clonidine and other drugs
Ethanol

VHL Genetics

- Inherited, autosomal dominant syndrome with a variety of benign and malignant tumors via “two-hit” model
  - Hemangioblastoma of the central nervous system
  - Retinal hemangioblastoma
  - Clear cell renal cell carcinoma
  - Pheochromocytoma
  - Endolymphatic sac tumors of the middle ear
  - Serous cystadenoma and neuroendocrine tumors of the pancreas
  - Papillary cystadenoma of the epididymis and broad ligament
- Incidence:1 in 36,000.
- Mean age of diagnosis: 26
- VHL gene located on chromosome 3p25. Acts as a tumor suppressor gene that regulates hypoxia-inducible factors

Clinical manifestations of von Hippel-Lindau disease

	Ages at diagnosis	Most common ages at dx	Frequency in patients CNS
CNS			
Retinal hemangioblastomas	0-68 yrs	12-25 yrs	25-60 percent
Endolymphatic sac tumors	12-46 yrs	24-35 yrs	10-25 percent
Cerebellar hemangioblastomas	9-78 yrs	18-25 yrs	44-72 percent
Brainstem hemangioblastomas	12-36 yrs	24-35 yrs	10-25 percent
Spinal cord hemangioblastomas	12-66 yrs	24-35 yrs	13-50 percent
Viscera			
Renal cell carcinoma or cysts	16-67 yrs	25-50 yrs	25-60 percent
Pheochromocytomas*	4-58 yrs	12-25 yrs	10-20 percent¶
Pancreatic tumor or cyst	5-70 yrs	24-35 yrs	35-70 percent
Epididymal cystadenomas	17-43 yrs	14-40 yrs	25-60 percent of males*
Adnexal papillary cystadenoma of mesonephric origin (broad ligament cystadenoma)	16-64 yrs	16-46 yrs	Estimated 10 percent of females

* Includes the 20 percent of lesions that occur outside the adrenal gland, also called paragangliomas.

¶ Frequency of pheochromocytoma varies widely depending on genotype.

VHL Genetics

A

VHL Disease Subtype	Pheochromocytoma	Cerebellar/Spinal Hemangioblastoma	Renal Cell Carcinoma	Representative Mutations
Type 1	low	high	high	Null
Type 2A	high	high	low	Tyr112His
Type 2B	high	high	high	Arg167Gln
Type 2C	high	none	none	Leu188Val
Chuvash Polycythemia	none	none	none	Arg200Trp

Large deletions and mutations in the *VHL* gene predicted to result in a truncated protein were associated with a much lower risk of pheochromocytoma than missense mutations (gain of function vs loss of function). These tumors are also more likely to only produce normetanephrines

Management Plans

- Optho/CNS: multiple retinal hemangioblastomas, retinal edema and right retinal detachment. 23 gauge pars plana vitrectomy, endolaser, membrane peeling by Dr. Blair
- RCC: q6 month observation
- PNET: ***
- Bilateral pheo: ***

Labs

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Adrenal Incidentaloma, Borderline Elevations of Urine or Plasma Metanephrine Levels, and the "Subclinical" Pheochromocytoma

James A. Lee, MD; Rasa Zarnegar, MD; Wen T. Shen, MD; Electron Kebebew, MD; Orlo H. Clark, MD; Quan-Yang Duh, MD

Table. Urine or Plasma Metanephrine Levels in All 42 Patients

Urine or Serum Metanephrine Levels	Pheochromocytoma, No. of Patients: Yes	Pheochromocytoma, No. of Patients: No
Elevated (>2× upper limit of normal)	11	0
Borderline (1-2× upper limit of normal)	3	7
Normal	0	21

In patients with borderline elevations, the mean ± SD tumor size was 5.4 ± 3.1 cm and 4.8 ± 1.9 cm for patients with and without pheochromocytoma, respectively

It is crucial to treat patients with borderline elevations of metanephrine levels as if they have a pheochromocytoma. For this reason, we recommend either alpha-blockade prior to resection for all patients with borderline elevations in metanephrine levels or further workup, per-

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PMID: 31397861

Comparison of Pheochromocytoma-Specific Morbidity and Mortality Among Adults With Bilateral Pheochromocytomas Undergoing Total Adrenalectomy vs Cortical-Sparing Adrenalectomy

Hartmut P. H. Neumann, MD,[1] Uliana Tsoy, PhD,[2] Irina Bancos, MD,[3] Vincent Amodru, MD,[4]

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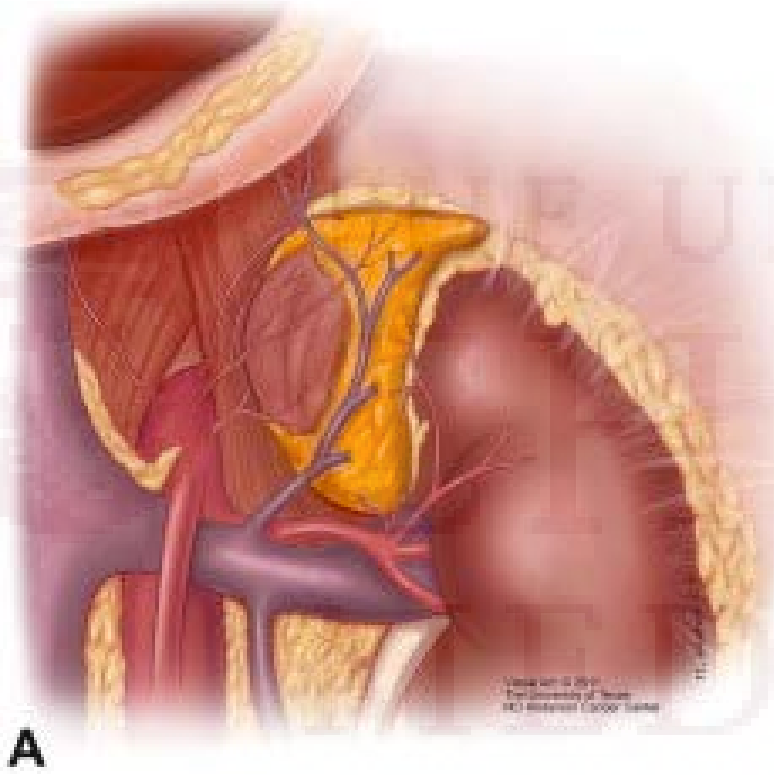

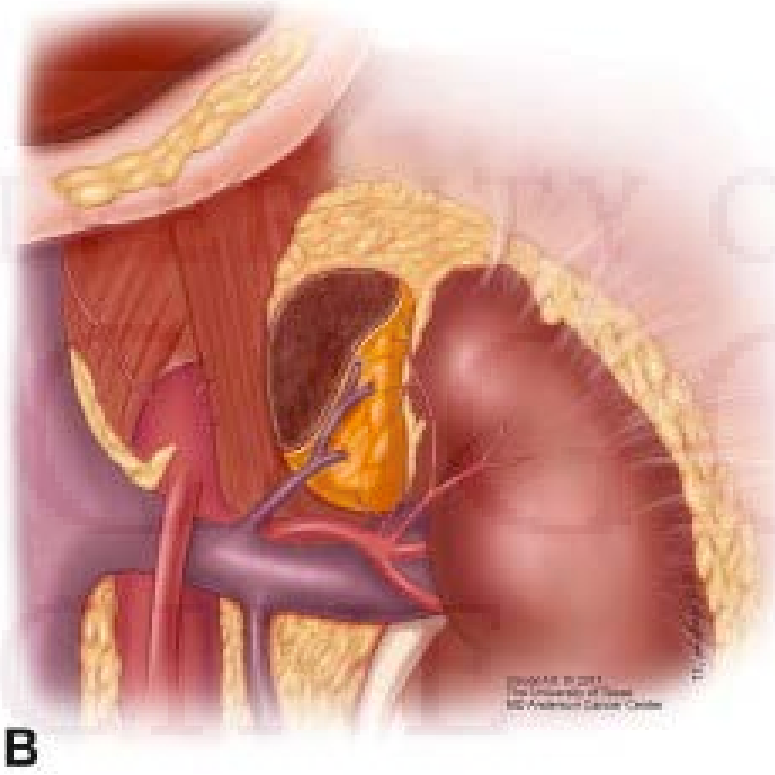

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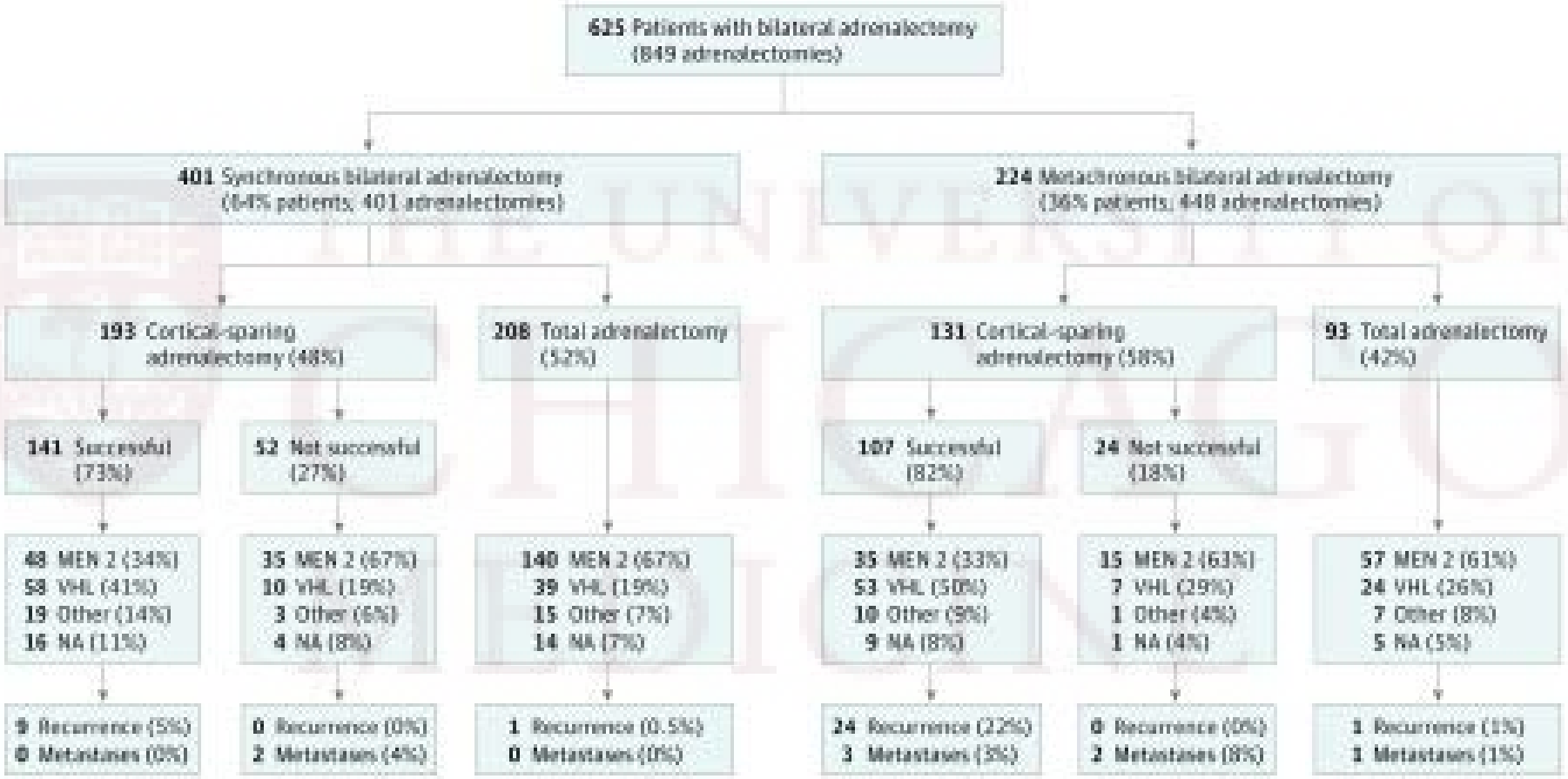
Total Versus Partial Adrenalectomy



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Total Versus Partial Adrenalectomy

- Cortical sparing more common since 2010
- Success not related to size of lesion
- Of those steroid dependent, 20% were from failed cortical sparing. This was more common in MEN2 (failure 38%) than VHL (failure 13%)
- VHL patients were at higher risk for development of recurrent ipsilateral pheochromocytoma compared to MEN 2 (23 of 191 [12%] vs 8 of 330 [2%]

Long-Term Outcomes of Surgical Treatment for Hereditary Pheochromocytoma

Presented at the Western Surgical Association Meeting, Tucson, AZ, November 2011.

Elizabeth G. Grubbs MD, FACS [a], Thereasa A. Rich MS [a], Chaan Ng MD [c], Priya R. Bhosale MD [c], Camilo Jimenez MD [b], Douglas B. Evans MS, FACS [d], Jeffrey E. Lee MS, FACS [a], Nancy D. Perrier MD, FACS [a]

- 15 of 49 patients (30%) who originally underwent unilateral partial adrenalectomy had pheochromocytoma develop in the contralateral adrenal gland, median of 8.2 years (range 1-20 years), and 10% in the ipsilateral gland

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Pheo: When to Operate

- Symptoms?
- Size?
- Metanephrine level?
  Endocrine Society 2014 guidelines x3-4 ULN diagnostic for paraganglioma/pheo
- Preoperative blockade

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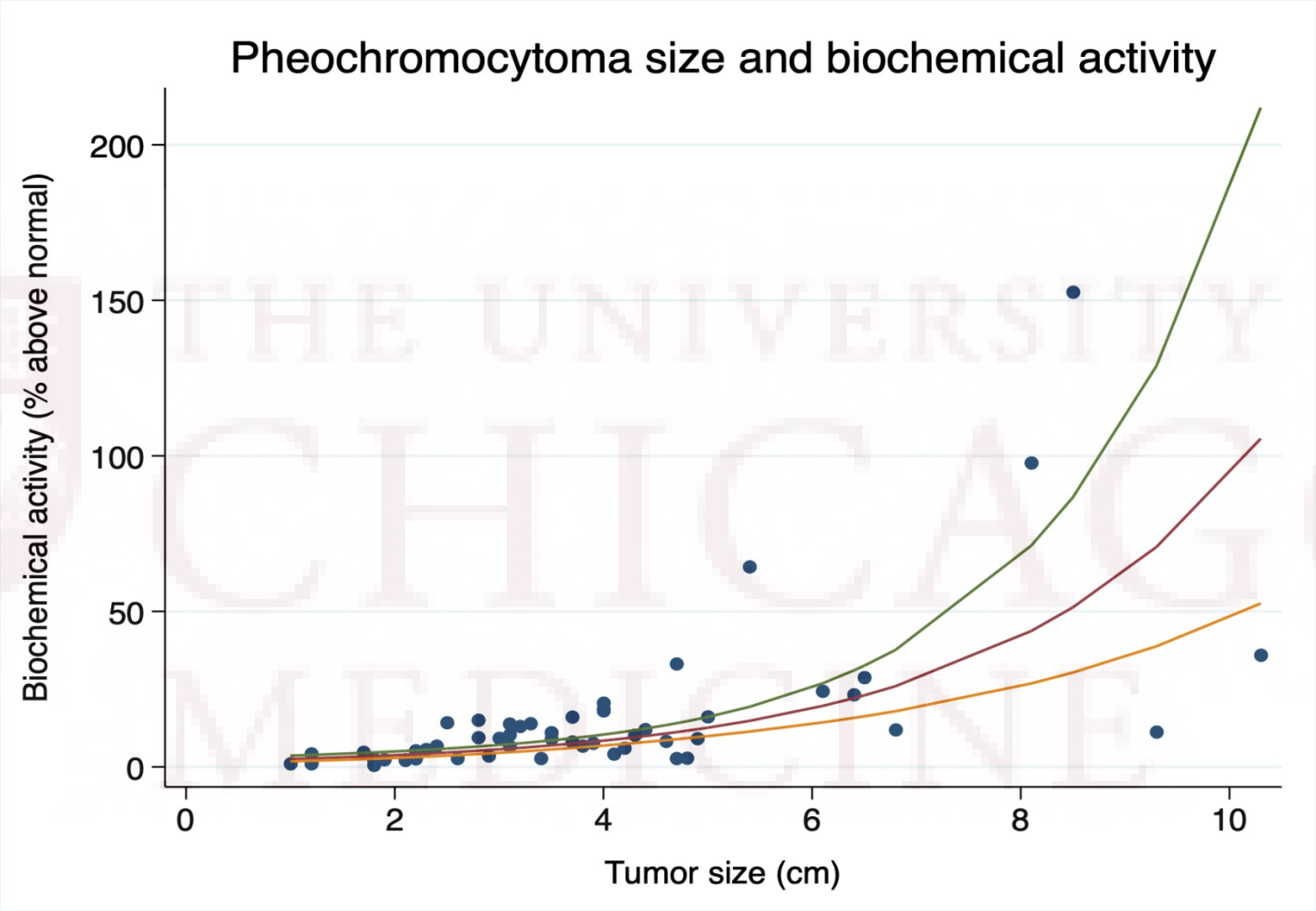

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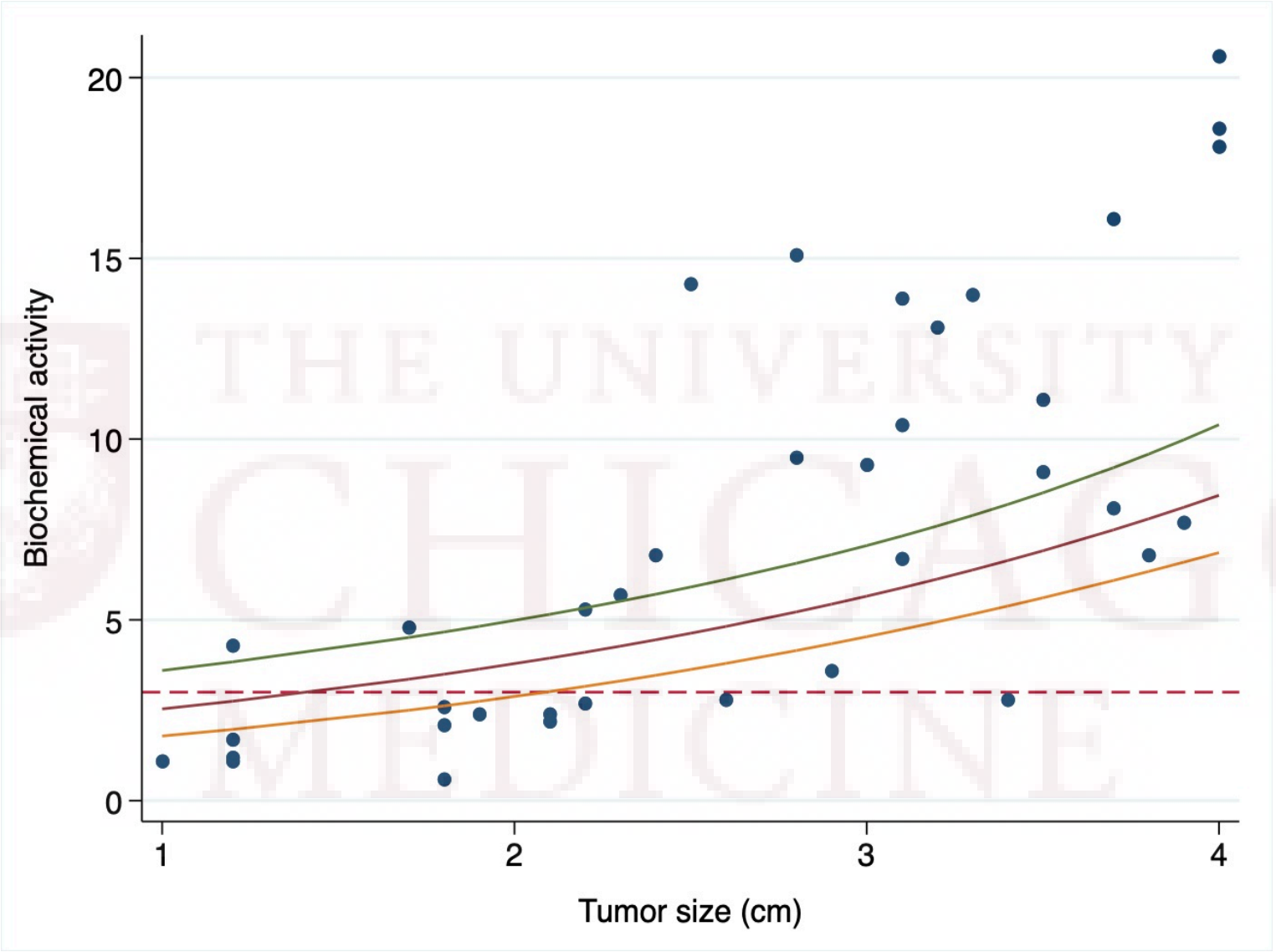

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Model suggests a 1.45cm pheo correlates with an average metanephrine level three times ULN

Management Plans

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- RCC: q6 month observation
- PNET: ongoing observation per 2019 NANETS guidelines
- Bilateral pheo: laparoscopic left partial adrenalectomy
  - Non-mobilization of planned remnant
  - Preservation of adrenal vein
  - Malignant pheo uncommon in this patient population

Pathology

- FINAL PATHOLOGIC DIAGNOSIS
  A. Left pheochromocytoma; adrenalectomy:
  - Pheochromocytoma (1.8 cm), see comment.

  B. Left pheochromocytoma #2; adrenalectomy:
  - Pheochromocytoma (0.7 cm), see comment.

  C. Additional pheochromocytoma; adrenalectomy:
  - Pheochromocytoma (2.6 cm), see comment.
  - Final margins free of tumor.

  D. Additional pheochromocytoma #2; adrenalectomy:
  - Pheochromocytoma (0.5 cm), see comment.
  - Final margins free of tumor

- The tumor exhibits no capsular or vascular invasion, no periadrenal adipose tissue extension, no necrosis, no cell spindling or monotony, no increased mitoses, and no atypical mitoses (PASS score = 2). Based on the histologic features, the tumor is predicted to have a benign or favorable behavior

Postoperative Labs

- Plasma Metanephrines: 0.21
- Plasma Normetanephrines: **1.0 (x1.1 ULN)**
- Plasma Epinephrine: 86
- Plasma Norpepinephrine: 703

2020 VHL Alliance Surveillance Guidelines

Surveillance for individuals with a pathogenic or likely pathogenic variant in *VHL*

Surveillance	Age to initiate	Interval	Comments
Dilated retinal examination	Before 1 year	Every 6 to 12 months	▪ Annually after age 30
History and physical examination by physician informed about VHL	1 year	Every year	
Blood pressure and pulse	2 years	Every year	
Metanephrines	5 years	Every year	▪ Plasma free metanephrines preferred but 24-hour urine fractionated metanephrines can be used
MRI of the brain and spine	11 years	Every 2 years	▪ Performed with and without contrast (without contrast if pregnant) ▪ Can be coordinated with MRI of the abdomen ▪ Include thin cuts through the posterior fossa and petrous temple bone ▪ One-time MRI of the internal auditory canal at age 15 years
Audiology	11 years	Every 2 years	
MRI of the abdomen	15 years	Every 2 years	▪ Performed with and without contrast (without contrast if pregnant) ▪ Assess kidneys, pancreas, and adrenal glands ▪ Can be coordinated with MRI of the neuroaxis

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Case #2

- 16 F w/ VHL (Dx age 2, no neuro manifestations), diagnosed with a PNET in 2018
- 3/2019: lap distal pancreatectomy/splenectomy
- PMH: Lupus anticoagulant w/ DVT/PE, on coumadin
- Right-sided adrenal nodule (1.3cm) noted on follow up MRI

Case #2

- 5/2020 plasma normetaphrines 206 (x1.4 ULN), metanephrine 28
- 7/2020 MRI Abd/Pel:
  - 1.5 x 1.3 cm right adrenal mass, slightly increased in size compared to 2019
  - 1.1cm segment 8 liver lesion consistent with metastatic lesion
  - Two enhancing foci along the right paravertebral soft tissues could represent additional neuroendocrine tumor such as paragangliomas, but are nonspecific and not significantly changed in size compared to 2018 MRI
- 6/2020 DOTATATE PET: Findings consistent with a radiotracer avid metastatic disease centered in the right adrenal gland and liver. No evidence of uptake in the retroperitoneum
- 12/2020 plasma normetaphrines 2.6 (x2.8 ULN), metanephrine < 0.2

Case #2

- 12/18/20: laparoscopic right partial adrenalectomy, resection of segment VIII liver lesion, microwave ablation of segment IVa lesion
- Pathology: Pheochromocytoma 1.9cm, Liver resection with metastatic NET, consistent with mets from Pancreatic primary
  - Synaptophysin, chromogranin, and S100 highlights the sustentacular cells, confirming the diagnosis of pheochromocytoma.
  - The tumor shows no capsular or vascular invasion, no extension into peri-adrenal tissue, no diffuse growth, no necrosis, no increase in cellularity or spindling, no cellular monotony or profound pleomorphism, no nuclear hyperchromasia and increased mitosis (PASS score = 0). Ki67 shows nuclear positivity in <2% of tumor cells. Overall, this pheochromocytoma is predicted to have a benign behavior

Case #2

- Repeat metanephrines
- Repeat MRI abdomen/pelvis in 2 months